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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,154	04/24/2002	George N. Cox III	4152-3-PUS	6320

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,154	COX ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *87 and 89* is/are withdrawn from consideration.

5)☒ Claim(s) *77,78,80,84-86,125-129,137 and 138* is/are allowed.

6)☒ Claim(s) *81-83, 90, 92-94, 96, 102, 104, 105, 131-135 and 139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 77,78,80-87,89,90,92-94,96,102,104,105,125-129,131-135 and 137-139.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Declaration under 37 CFR 1.131 of Dr. George Cox submitted on 25 March 2009, and the Declaration under 37 CFR 1.131 of Dr. Daniel Doherty, submitted on 15 April 2009 are acknowledged. Applicant's amendment of the claims filed 25 March 2009 has been entered.

Claims 1-76, 79, 88, 91, 95, 97-101, 103, 106-124, 130 and 136 have been cancelled. Claims 77, 78, 80-87, 89, 90, 92-94, 96, 102, 104, 105, 125-129, 131-135 and 137-139 are pending. Claims 87 and 89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 77, 78, 80-86, 90, 92-94, 96, 102, 104, 105, 125-129, 131-135 and 137-139 are under examination.

Claim Rejections Withdrawn

The rejection of claims 126 and 137 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to define the sequences for erythropoietin and immunoglobulin (Ig) domain by either a SEQ ID or specifying the species where the sequences are

generated, is withdrawn in response to Applicant's amendment of the claims to recite a human erythropoietin and a human immunoglobulin (Ig) domain.

The rejection of claims 68, 77, 78, 80-86, 125-129 and137 under 35 U.S.C. 102(e), as being anticipated by Strom et al. (US 6,165,476), is withdrawn in response to Applicant's amendment of the independent claims 125, 126 and 137 to limit the Ig domain to be the full length of IgG-Fc, IgG-C_H or IgG-C_L.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 90, 92-94, 96, 102, 104, 105, 131, 132 and 139 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (U. S. Patent No. 6,485,726 B1, which was filed on 24 July 1998, and has a priority date on 17 January 1995), in view of Mapelli et al. (U. S. Patent No. 5,519,115, issued on 21 May 1996), for reasons made of record.

Applicant argues that Blumberg et al. (U. S. Patent No. 6,485,726) is not effective prior art against the invention as claimed, because the claimed subject matter was invented by the present inventors prior to the effective date of the material referenced in columns 12 and 13 of the '726 patent regarding construction of the EPO-Fc fusion.

Applicant argues that the material does not appear in his priority document of U. S. Patent No. 6,030,613; thus, the effective prior art date for this new disclosure is the filing date of 6,485,726 (24 July 1998). Applicant provided a Declaration under 37 CFR § 1.131 executed respectively by the inventors of the instant application, George Cox and Daniel Doherty, which declares conception of the invention as claimed in these claims at a date prior to July 24, 1998, followed by diligence beginning from a date prior to July 24, 1998, to the constructive reduction to practice of the invention as claimed in the presently rejected claims.

Applicant further argues that even if U. S. Patent No. 6,485,726 was an effective reference, Blumberg et al. does not actually teach or suggest an EPO-IgG fusion protein as claimed. On pages 14-15 of Applicant's remarks, Applicant argues that Blumberg et al. only mentions an Epo-IgG fusion protein in a hypothetical discussion; there is no example describing the construction of an Epo fusion protein; and it is not clear that Blumberg et al. ever made the fusion protein or that the fusion protein was biologically active. Applicant argues that the Fc fragment used in Blumberg et al. is not the full-length, and it misses the CH1 domain as a result of utilizing a *Sal I* restriction site. Applicant also argues that Blumberg et al.'s Epo fusion protein would be separated from the Fc domain by at least 4 amino acids (Ala Ala Ala Val), instead of 3 amino acids. Applicant argues that Blumberg et al. does not teach or suggest a human EPO fusion protein linked to a full-length human immunoglobin domain via a peptide linker. Applicant argues that the secondary reference, Mapelli et al., is not directed to the production of fusion proteins in general, let alone an EPO-Ig fusion protein, which is a

fusion of two large proteins with very different structures. Applicant argues that the EPO-Ig fusion proteins are far more complex than the simple oligomers of the shorter peptides contemplated by Mapelli et al, because EPO-Ig fusion proteins also interact to form disulfide-linked dimers, which can negatively affect their bioactivity. Applicant argues that EPO and Ig proteins can not properly be considered to be peptide monomers as used by Mapelli et al.; and that Mapelli, et al. does not teach or suggest the use of full-length proteins and requires that the bridge promotes inter-monomer interactions. Applicant argues that there is no reason to look to Mapelli et al. for guidance on a form of peptide linker in an EPO-Ig Fusion.

Applicants' argument has been fully considered but has not been found to be persuasive. The Declaration under 37 C.F.R. § 1.131 executed respectively by George Cox and Daniel Doherty filed 3/25/2009 and 4/15/2009 has been fully considered, however, it is insufficient to overcome the rejection for the following reasons.

Applicant has provided the Declaration under 37 CFR § 1.131 executed by the inventors of the instant application, George Cox and Daniel Doherty, which declares conception of the invention at a date prior to July 24, 1998 (the filing date of US 6,485,726), followed by diligence beginning from a date prior to July 24, 1998, to the constructive reduction to practice of the invention as claimed in the presently rejected claims. While the Declaration under 37 CFR § 1.131 antedates the filing date of US 6,485,726 (filed July 24, 1998), however, it fails to antedate the priority document of US 6,485,726 which contains support for an Epo-Ig Fc conjugate.

U. S. Patent No. 6,485,726 B1 (Blumberg et al.) was filed on 24 July 1998, which claims priority as continuation-in-part for Application No. 08/899,856, filed on 24 July 1997, (now U. S. Patent No. 6,030,613); Application No. 08/578,171, filed on 29 December 1995, (now abandoned); and Application No. 08/374,159, filed on 17 January 1995, (now U. S. Patent No. 6,086,875). The erythropoietin-IgG Fc conjugate is supported in the priority documents. For example, US 6,030,613 (filed on 24 July 1997) teaches conjugating an erythropoietin with an FcRn binding partner such as the Fc fragment of Ig (col. 13, line 42-43; col. 6, section 4.1). Also, US 6,086,875 (filed on 17 January 1995) teaches conjugating an FcRn binding partner, e.g., the Fc fragment of IgG (col. 3, lines 46-49), to a supplementary potentiating agent, such as an erythropoietin (col. 4, line 9-14; col. 9, line 10). The '875 patent further teaches including linkage through peptide bonds for covalent linking to an FcRn partner (col. 7, lines 38-47). Therefore, the priority documents of US 6,485,726 disclose the erythropoietin-IgG Fc conjugate, and US 6,485,726 benefits the filing dates of the priority documents.

With regard to Applicant's argument that Blumberg et al. does not actually teach or suggest an EPO-IgG fusion protein as claimed, and only mentions an Epo-IgG fusion protein in a hypothetical discussion, Blumberg et al. teaches conjugating an erythropoietin (EPO) to an Fc fragment of an immunoglobulin, and the covalent linking can be achieved by including a linkage (linker). At the time the invention was made, both erythropoietin (e.g., human erythropoietin) and the Fc fragment of an immunoglobulin were well characterized (as evidenced in US 4,703,008, which is incorporated-by-reference in the Blumberg et al.'s 726 patent). Further, construction of a

fusion protein by recombinant technology was well established (as evidenced in the priority document US 6,086,875, col. 7, lines 38-47). Even though Blumberg et al. does not exemplify in the Examples of the priority documents to make an EPO-IgG fusion protein, one of ordinary skill in the art would recognize that Blumberg et al. expressly teaches such an fusion protein, and one of ordinary skill in the art would know how to make such an fusion protein based on the disclosure of Blumberg et al. and the state of art at the time the invention was made. In other words, Blumberg et al. does not "*only mentions an Epo-IgG fusion protein in a hypothetical discussion*".

With regard to Applicant's argument that the Fc fragment used in Blumberg et al. is not the full-length, and it misses the CH1 domain as a result of utilizing a *Sal I* restriction site, in referencing the FcRn binding partner that can be used for making a fusion protein, Blumberg et al. teaches that it is preferably an Fc fragment of IgG (see priority document US 6,086,875, col. 3, lines 46-49). Thus, Blumberg et al. specifically teaches the using of the entire Fc fragment.

With regard to Applicant's argument that Blumberg et al.'s Epo fusion protein has a 4-amino acid (Ala Ala Ala Val) linker, instead of a 3-amino acid linker, independent claims 90 and 139 recite the peptide linker between 2-7 amino acids. Further, the claimed amino acid compositions for the linker that links two polypeptides are taught and suggested by Mapelli et al. Applicant's argues that the EPO-Ig fusion proteins are far more complex than the simple oligomers of the shorter peptides contemplated by Mapelli et al, and there is no reason to look to Mapelli et al. for guidance on a form of peptide linker in an EPO-Ig Fusion. Mapelli et al. teach the use of a small bridge, e.g.,

small bridges of 5 amino acids or less, in the construction of oligopeptides (col. 24, lines 21-24). Mapelli et al. teach that these small bridges prevent disadvantageous steric hindrance between discrete monomers, and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations (col. 24, lines 7-20). Mapelli et al. teach that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energenically stable bond structure (col. 24, lines 53-63). Mapelli et al. further give several example of such Gly-rich linkers, e.g., bridges having 2 and 4 amino acids, Ser-Gly-Gly-Ser (identical to SEQ ID NO: 1) (col. 25, line 6), and Ser-Gly (col. 27, line 23). It would have been obvious to one of the ordinary skill in the art to take the advantages as described in Mapelli et al. for the small bridges, these advantages include: preventing disadvantageous steric hindrance between discrete monomers; providing a sufficient degree of flexibility to allow for the formation of advantageous conformations; and not sterically hindering any potential folding of the oligomer and participating in energenically stable bond structure. These properties are desirable when making any functional fusion protein, in particular, an Epo protein that requires proper tertiary structure and folding for biological activity. Therefore, it would have been *prima facie* obvious to one of the ordinary skill in the art at the time the invention was made to use the small Gly-rich linkers, such as Ser-Gly-Gly-Ser (SEQ ID NO: 1) or Ser-Gly, for conjugating an EPO with the Fc fragment. One of ordinary skill in the art would have been motivated to do so, because preventing steric hindrance between discrete monomers, and providing a sufficient degree of flexibility to allow for the formation of advantageous conformations is desirable for any

fusion protein, no matter it is an oligopeptide or oligopolypeptide. Mapelli et al. teach that small Gly-rich linkers meet these requirements. Further, a correct conformation provides the functions and activities of the molecules, no matter how complex they are.

Claims 133-135 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (US 6,485,726 B1), in view of Mapelli et al. (US 5,519,115), and further in view of Qiu et al. (J. Biol. Chem., 1998, May 1,273(18):11173-11176), for reasons made of records.

Applicant argues that Qiu et al. reported that EPO-EPO fusion proteins joined by peptide linkers of 3-7 glycine residues have significantly reduced biological activities (4-10-fold) relative to wild-type EPO. Applicant argues that Qiu et al. makes conflicting statements concerning the bioactivity of their EPO dimer proteins; specifically, Qui et al. does state that Epo dimer proteins had similar activities as EPO (page 1174, column 2, paragraph just below Fig. 2) based on the use of a radioimmunoassay (RIA) to measure protein Epo concentration in the conditioned media; but later on page 11175, column 1, (in the section: "*Immunoblot of the Engineered Tag for Confirmation of Protein Concentration*") Qiu et al. states that the protein concentrations determined by RIA are incorrect and an underestimate of the amount of protein in the Epo dimer conditioned media. Therefore, Applicant asserts that the bioactivity numbers Qiu et al. reported in the earlier part of the reference are incorrect. Applicant also argues that Qui et al. reports activities expressed in mIU/ml of conditioned media (wild-type Epo 105 mIU/ml and dimeric Epo 185 mIU/ml); however, it is known to those skilled in the art that it is critical to know how much of the Epo protein there is per mL of conditioned media.

Applicant argues that initially Qiu et al. quantitated the protein amount by RIA and got incorrect numbers, and later, on page 11175, Qiu et al. got better quantitation by doing Western blots (see Fig.5 of Qiu, et al.); and on page 11175 column 2 line 4 of text Qiu, et al. admits that the RIA underestimates the concentration of Epo dimers by a factor of 2-5. Based on these, Applicant asserts that the Epo dimer protein in Qui et al. had reduced biological activity compared to monomeric Epo.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Independent claim 90, which claims 133-135 depends from, recites the fusion protein has an EC_{50} within 4 fold of the non-fused EPO on a molar basis in an EPO-dependent *in vitro* bioassay, and claims 134 and 135 further recite an EC_{50} of less than about 10 ng/ml or 4 ng/ml. The data shown in Fig. 2 and the text description on pp. 11174 (section: "*Epo-dependednt Cell Proliferation*") clearly shows that the Epo dimer proteins linked by 7 glycine residues had similar activities as monomeric WT EPO when quantitated as mIU/ml (i.e., wild-type Epo 105 mIU/ml and dimeric Epo 185 mIU/ml). Even considering the different quantitation methods of Qiu et al. and the instant application, and given a factor of 2-5 fold underestimation of quantitation measured as mIU/ml, the biological activities of the dimeric EPO are still "within 4 fold of the non-fused EPO on a molar basis in an EPO-dependent *in vitro* bioassay".

With regard to the specific EC_{50} recited in claims 134 and 135 (i.e., less than about 10 ng/ml or 4 ng/ml), these limitations do not render the invention patentable. "Mere recognition of latent properties in the prior art does not render nonobvious an

otherwise known invention" (see MPEP 2145 [R-2] and *in re* Wiseman, 596 F.2d 1019, 201 USPQ 658). Applicant has provided quantitative data, however, it has been established that the invention is obvious. As such, Applicant has worked out experimental details that are immaterial to the claimed invention, since the use of a peptide sequence with 7 glycine residues has been shown obvious over the prior art and to a person of ordinary skill in the art as a linker for construction of a dimeric EPO, and the resulting molecule has a biological activity falling within the range as recited in the claims. Further, as a practical matter, the Patent Office is not equipped to manufacture and quantitation of products put before it and then obtain prior art products and make physical comparisons therewith." In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

For these reasons, the claims are prima facie obvious over the cited references.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a nucleic acid encoding the fusion protein, does not reasonably provide enablement for *in vivo* transfection.

The claims recite a host cell, e.g., an eukaryotic cell or a mammalian cell, transfected or transformed with the nucleic acid encoding the fusion protein. The claim language does not limit that the host cell are isolated, and thus, it reads on *in vivo* transfection. The specification on page 16, Example 2, discloses recombinant expression of the fusion protein using cultured mammalian cells, e.g., COS cells. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise the nucleic acid sequence encoding the fusion protein in an animal. Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as written are not enabled. This rejection could be overcome by addition of the limitation wherein the host cells are isolated.

Conclusion

CLAIMS 77, 78, 80, 84-86, 125-129, 137 AND 138 ARE ALLOWABLE.

CLAIMS 81-83, 90, 92-94, 96, 102, 104, 105, 131-135 AND 139 ARE REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nicole, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
June 29, 2009

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646